REMARKS

Formal Matters

Claims 43-47 and 49-60 are pending in the application. Claims 43,44,46,47,49-52 are amended and new claim 60 is added. The amendments are fully supported by the specification as filed, and accordingly, do not introduce new matter. Examples of support for each of the amended or new claims are found at the following locations in the specification:

Claim 43: page 3, lines 2-8; claims as originally filed;
Claim 46: page 20, lines 13-15;
Claim 47: page 21, lines 12; page 22, lines 19-29;
Claim 49: page 3, lines 9-13; page 4, lines 2-4; claims as originally filed;
Claim 50: page 3, lines 13-16; page 4, lines 2-4; claims as originally filed;
Claim 51: claims as originally filed;
Claim 52: claims as originally filed;
Claim 60: page 21, lines 13-23; page 22, line 30-page 23, line 6.

The specification has been amended to update the priority information. And a new CRF is submitted to replace the damaged one, pursuant to the Notice to Comply form accompanied with the Office Action.

Claim Objections

Claim 51 is objected to because of a typographical error in identifying the corresponding light and heavy chain sequences recited in the claim. Applicants submit that the claim was amended to correct the error in a Supplemental Amendment submitted January 9, 2003.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 47, 49-50 are rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not enable an antibody as broadly claimed in a method of inhibiting angiogenesis. According to the Examiner, the claims are broadly drawn to a method of inhibiting VEGF-induced angiogenesis with an antibody with specific CDRs of a light chain and any CDRs of a heavy chain, or an antibody with specific CDRs from a heavy chain and any CDRs from any light chain (emphasis added by the applicants). Meanwhile, the specification allegedly provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain

variable regions. Furthermore, according to the Examiner, it is unlikely that such antibodies have the required binding function or can be used in the claimed methods, because it is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function.

Applicants submit that claim 47 has been amended to further clarify that the humanized anti-VEGF antibody used in the claimed method comprises a heavy chain and a light chain, wherein the heavy chain variable domain comprises four FRs and three CDRs as a contiguous sequence represented by the formula: FR1-CDRH1-FR2-CDRH2-FR3-CDRH3-FR4, wherein the four FRs are derived from a consensus human antibody heavy chain framework region sequence and the three CDRs are derived from a non-human anti-VEGF antibody, and wherein the light chain variable domain comprises four FRs and three CDRs as a contiguous sequence represented by the formula: FR1-CDRL1-FR2-CDRL2-FR3-CDRL3-FR4, wherein the four FRs are derived from a consensus human antibody light chain framework region sequence and the three CDRs are derived from the non-human anti-VEGF antibody. Thus, the amended claim 47 is directed to a humanized anti-VEGF antibody with heavy and light chain variable domains in a sequence formula that is well known as sufficient to provide intact antigen-binding. Furthermore, all the CDRs are derived from the same non-human anti-VEGF antibody, thus maintaining the human VEGF binding specificity in the resulting humanized antibody. Claims 49-50 further recite specific CDR sequences for both the light and heavy chain variable domains of the humanized anti-VEGF antibody.

With regard to the Examiner's concern, citing Rudikoff et al., that minor changes in the variable domains, particularly in the CDRs, may dramatically affect antigen-binding function, Applicants submit that the present application provides adequate teachings with ample working examples as to how to make amino acid changes in the variable domains in order to obtain humanized anti-VEGF antibodies with desirable antigen binding affinity and biological activities. For example, Specification at pages 21-23 teaches that the FRs of the humanized antibody which is derived from human FRs may preferably contain residue substitutions wherein the human FR residue(s) is replaced by corresponding non-human residue or a totally different residue, and the resulting antibodies can be subject to, for example, phagemid library display for selection of antibodies having desired antigen-binding affinity. Moreover, the specification teaches further making variants of a humanized antibody in order to obtain even stronger binding affinity. See,

for example, pages 27-30. Example 3 on pages 67-80 also describes how to make amino acid substitutions in both FRs and CDRs in order to obtain "affinity matured" variants with higher binding affinities.

Indeed, the non-limiting working examples of the specification provide detailed teachings for the claimed invention. The Examples describe three different methods for making different sets of anti-VEGF antibodies, all having individual humanized antibodies or antibody variants with desirable properties from therapeutic perspectives, as presently claimed. Specifically, Example 1 describes methods and materials that resulted in a series of humanized anti-VEGF F(ab) variants. One of these variants, F(ab)-12, exhibited a K_d value of $1.8x\ 10^{-9}M$ in a VEGF binding assay. Table 3 on page 57. F(ab)-12 was used to construct a full length mAb, rhuMAb VEGF, which also exhibited the desirable properties as claimed. Example 2 describes methods and materials that resulted in a series of humanized Fab variants selected from a humanized A4.6.1 phagemid Fab library. One of the phage selected clones, hu2.10V, exhibited a K_d value of $9.3x10^{-9}M$ in a VEGF binding assay. Table 7 on page 67. Lastly, Example 3 describes using methods of CDR randomization, affinity maturation by monovalent Fab phage display, and cumulative combination of mutations to enhance the affinity of a humanized anti-VEGF antibody. As the result, several antibodies with high binding affinity were created, including Y0313-1, Y0238-3, and Y0317. Table 15 on page 80 and discussion on page 81. All the above exemplified antibodies or antibody variants have distinct sequence structures, yet exhibited similar desirable properties that are encompassed by the present claims.

In view of the amendments and the above remarks, Applicants submit that the claims are in compliance with 35 USC §112, first paragraph, and respectfully request the rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 43-47, 49-50 and 53-56 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ferrara et al. WO 94/10202 ("Ferrara et al"), and further in view of Adair et al. WO91/09967 ("Adair et al") and Yelton et al. (1995)*J. Immn.* 155:1994-2004 ("Yelton et al"). Claims 43-47, 49-50 and 53-59 are also rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ferrara et al. and further in view of Adair et al. and Yelton et al. as applied to claims 43-47, 49-50, 53-56, and further in view of Lopez et al. (1996) Invest. Opthal. and Visual Sci. 37:855-868 ("Lopez et al") concerning the role of VEGF in the progression of ARMD.

According to the Examiner, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of inhibiting VEGF-induced angiogenesis in a subject with cancer or AMD, by administration of a humanized antibody of Ferrara et al humanized by the methods of Adair et al and Yelton et al. Moreover, the Examiner took the position that the antibody so produced would have the binding and inhibition characteristics claimed in the present invention. Applicants respectfully traverse these rejections.

Claim 43 has been amended to a method for inhibiting VEGF-induced angiogenesis in a subject, comprising administering to said subject an effective amount of a humanized anti-VEGF antibody which (a) binds human VEGF with a K_d value of no more than about 1×10^{-8}M; (b) has an ED50 value of no more than about 5nM for inhibiting VEGF-induced proliferation of endothelial cells *in vitro*; and (c) inhibits VEGF-induced angiogenesis *in vivo*, wherein 5mg/kg of said humanized antibody inhibits at least about 50% of tumor growth in an A673 *in vivo* tumor model. Thus, to render the present claims obvious over the cited references, it must be shown that one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to produce a humanized anti-VEGF antibody having all of the above-recited properties. Applicants submit that the teachings of the cited references, even if combined, would not have rendered obvious a humanized anti-VEGF antibody with the desired VEGF binding affinity as presently claimed, much less the additionally claimed potencies both *in vitro* and *in vivo* (i.e., elements (b) and (c) of claim 43).

As disclosed in the specification of the present application, while non-human anti-VEGF neutralizing antibodies capable of suppressing angiogenesis related conditions (including the growth of a variety of human tumor cell lines in nude mice) and uses thereof were known in the art, the present invention is directed to humanized anti-VEGF antibodies with desirable properties from a therapeutic perspective. See specification at page 2, lines 19-29. The invention was the result of a series of experiments employing different approaches for humanizing an anti-VEGF antibody. One of ordinary skill in the art applying the general methods of Adair et al or Yelton et al to the anti-VEGF antibody of Ferrara et al would not have had reasonable expectation of success in producing a humanized anti-VEGF antibody having both the binding affinity and the inhibition potencies as currently claimed.

In particular, applicants point out that it has been known in the art, and even acknowledged in the cited references Adair et al and Yelton et al, that an antibody with high

binding affinity to its antigen does not necessarily exert desired efficacy when used in the context of cultured cells or *in vivo* therapeutic treatment. For example, Adair et al discloses a method of humanization combining CDR grafting with framework residue substitutions, based on studies of an anti-CD3 antibody OKT3. When tested for biological activities, even those modified antibodies with increased antigen binding affinities behaved differently in an unpredictable manner. In Example 5 (pages 61-64), for example, a number of murine anti-TGF-α mAbs were CDR-grafted (and FR residues swapped) according to the protocol used for OKT3 antibodies. Some of the resultant variants showed binding affinities similar to that of the murine or chimeric counterpart antibodies. These variant antibodies were then assessed in an L929 cell competition assay in which the antibody functionally competes against the TNF receptor on L929 cells for binding to TNF in solution. The results showed that while some of the resultant antibodies were able to compete well in the L929 assay, many others failed to effectively compete with and block the TNF receptor-ligand interaction. Specifically, gL221/gH341, the humanized version of 61E71, was approximately 10% as active as murine 61E71 (page 61); the humanized version of hTNF3 bound well to TNF-α, but competed very poorly in the L929 assay (page 63); and the humanized 101.4 antibodies were at least an order of magnitude less able to compete for TNF against the TNF receptor on L929 cells (page 64). Thus, the Adair et al reference itself showed that increased binding affinity of a humanized antibody as a result of using the methods taught therein can not predict improved competitive activity in a cell assay.

Yelton et al describes affinity maturation of a chimeric anti-carcinoma antibody, BR96, by codon-based mutagenesis. BR96 is a mAb recognizing Lewis Y (Le^y)-related antigens expressed on the surface of many human carcinomas. The affinity mutants of BR96 were tested for their binding affinities to either an enzyme conjugate of synthetic Le^y tetrasaccharide (sLe^y) serving as an isolated antigen, or carcinoma cell lines expressing on their surface the Le^y antigen. The results provided by Yelton et al clearly show that the binding affinity to sLe^y does not always correlate with the binding affinity to tumor cells with Le^y expressed and bound on their surface. For example, a mutant clone M4 was shown to bind sLe^y with a 3-4 fold greater reactivity than M1 (another mutant), and an approximately 15-20 fold increase compared with the BR96 parent. Yet it did not show any improvement over M1 in binding to H3396 tumor cell membranes. Pages 1999-2000. Thus, antibody mutants generated according to Yelton et al would not necessarily have desired binding affinity to an antigen in a native state, much less any therapeutic efficacy. Indeed, the authors of the references went on to postulate that increasing the affinity of an

antibody (specific to a tumor antigen) may not bring a therapeutic advantage in treating tumors. Page 2002, bottom of the left column.

In light of the claim amendments and for the reasons stated above, the claimed invention was not obvious to one of ordinary skill in the art at the time the invention was made, and removal of the rejections under 35 U.S.C. §103(a) is respectfully requested.

SUMMARY

Claims 43-47; 49-59 and new claim 60 are pending in the application.

If in the opinion of the Examiner, a **telephone conference** would expedite the prosecution of the subject application, the Examiner is **strongly encouraged** to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and petition for a three month extension of time and fees. In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Respectfully submitted,

GENENTECH, INC.

Date: July 17, 2003

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